

**REMARKS**

Claims 1-51 and 76-144 are pending herein. By the Office Action, claims 4, 13-14, 26-49, 76-110 and 122-144 are withdrawn from consideration; and claims 1-3, 5-12, 15-25, 50-51, and 111-121 are rejected under 35 U.S.C. §103. By this Amendment, claims 1, 26 and 76 are amended and claim 33 is canceled. Support for the amendments to claims 1, 26 and 76 can be found in the specification at page 22, lines 11-13. No new matter is added.

I. **Restriction/Election Requirement**

Claims 4, 13-14, 26-49, 76-110 and 122-144 are withdrawn from consideration as subject to Restriction and Election Requirements.

A. **The Requirements are Clearly Improper and Must be Withdrawn**

Applicants again assert that both the Restriction Requirement and the Election of Species Requirement are clearly improper, and should be withdrawn. The Requirements are improper at least because there would be no burden on the Examiner to search and examine the full scope of the pending claims.

Applicants respectfully assert that search and examination of the entire application could be conducted without undue burden on the Examiner, thus avoiding delay and expense to Applicants. This is evidenced by the fact that the Patent Office has already searched and examined the full scope of all of the original claims. The application was already subjected to a first Restriction Requirement, mailed January 3, 2001, to which Applicants filed a response on January 24, 2001. Based on Applicants' response, the Examiner previously indicated that the original Restriction Requirement was withdrawn, and all of the pending claims were examined on the merits. See April 6, 2001, Office Action at page 2.

Since that first Restriction Requirement, the Patent Office has issued three Office Actions, all of which addressed all of the pending claims on the merits. See Office Actions dated April 6, 2001, October 9, 2001, and March 13, 2002. Applicants timely responded to

each of the Office Actions and, in response to an Advisory Action, filed a Request for Continued Examination on November 13, 2002.

As evidenced by the already lengthy prosecution history, the Patent Office has already searched and examined all of the pending claims, on at least three separate occasions. Because all of the claims have been searched and examined, there should be no further substantial burden on the Examiner to continue to search and examine the entire claimed invention. Maintaining the Restriction and Election of Species Requirements would thus only work a manifest injustice upon Applicants. The Requirements should thus be withdrawn.

B. The Requirements are Traversed

With respect to the Restriction Requirement, Applicants continue to assert that the basis for the Restriction Requirement is improper, at least based on the inter-relation between the identified inventions, and the prior search and examination of this application. Applicants request reconsideration and withdrawal of the Restriction Requirement, and reserve the right to Petition the propriety of the Restriction Requirement.

With respect to the Election of Species Requirement, Applicants understand that upon search, examination and allowance of the elected species, search and examination will continue as to the non-elected species within the scope of the generic claims.

II. Rejection Under 35 U.S.C. §103

Claims 1-3, 5-12, 15-25, 50-51, and 111-121 are rejected under 35 U.S.C. §103(a) over Leung (WO 96/40797) in view of Engelson. Applicants respectfully traverse this rejection.

A. Independent Claim 1 and its Dependent Claims

Independent claim 1 is directed to a method of applying at least one agent selected from the group consisting of bioactive materials, flavorants, polymerization initiators, and polymerization rate modifiers to an applicator tip for an adhesive applicator, comprising:

dissolving or dispersing said agent in a low boiling point solvent to form a solution; applying said solution to said applicator tip; and drying said applicator tip; wherein the low boiling point solvent comprises methanol, and wherein said applicator tip comprises a porous, absorbent, or adsorbent material. Claims 2-3, 5-12, 15-25, and 111-121 ultimately depend from claim 1. Such methods are nowhere taught or suggested by the cited references.

1. Leung Does Not Teach or Suggest Using Methanol

An aspect of the claimed invention is that while the various materials may be applied to the applicator tip in a number of different ways or in a number of solutions, the use of a solution comprising methanol provides a distinct advantage. In particular, as described in the specification, the present inventors discovered that the use of methanol, alone or as a component of a mixture of low boiling point solvents, provides an unexpectedly superior distribution profile of the material on, and within, the applicator tip, and provides desirable setting characteristics. Specification at page 6, lines 2-6. In particular, the superior distribution profile allows a shorter or equivalent setting (polymerization) time of the dispensed monomeric adhesive while avoiding tissue damage due to the highly exothermic polymerization reaction. Specification at page 6, lines 6-9.

Leung fails to teach or suggest applying the specified agents to an applicator tip using a solvent comprising methanol. At most, Leung discloses that "the applicator tip material may be porous, absorbent or adsorbent in nature to enhance and facilitate loading of the initiator on or within the applicator tip." Page 15, lines 15-18. The reference then discloses that the initiators "may be applied to a surface portion or to the entire surface of the applicator tip, including the interior and the exterior of the tip." Page 15, lines 35-38. Finally, Leung discloses that a liquid medium used to apply the initiator "may include non-aqueous solvents, such as ether, acetone, ethanol, pentane or mixtures thereof, or may include aqueous solutions. Preferably the liquid medium is a low boiling point solvent." Page 17, lines 24-28.

Thus, while Leung discloses that a low boiling point solvent can be used, and discloses various suitable solvents, the reference does not teach or suggest the use of a low boiling point solvent that comprises methanol, as claimed. Nor does Leung teach or suggest that methanol could or should be used in place of or in addition to any of the specified solvents. Accordingly, Leung would not have rendered obvious to one of ordinary skill in the art the invention of independent claim 1, and the claims dependent therefrom.

2. Engelson Does Not Overcome the Deficiencies of Leung

The Office Action admits that Leung does not teach the use of methanol as the low boiling solvent for applying the specified agents to an applicator tip. However, the Office Action cites Engelson for allegedly teaching the equivalence of ether, methanol, ethanol, and propanol. The Office Action thus asserts that it would have been obvious for one of ordinary skill in the art to have used methanol in the methods of Leung, to practice the claimed invention. Applicants respectfully disagree.

Engelson is directed to the application of a thin, very slippery polymer coating to the outer surface of a catheter to assist in use of the catheter. The coating is formed by applying to the catheter a solution of polymer or oligomer in solvent, optionally with an initiator applied at the same or a later time. See Engelson at Abstract and col. 4, lines 31-67.

However, Engelson does not disclose at least the instant claim limitations of applying the at least one agent to an applicator tip for an adhesive applicator, and where the applicator tip comprises a porous, absorbent, or adsorbent material. At most, Engelson teaches applying a solution of solvent, polymer or oligomer, and optional initiator to the outer surface of a solid catheter. The catheter is not an applicator tip, is not an applicator tip for an adhesive applicator, and does not comprise a porous, absorbent, or adsorbent material, as claimed. These limitations are expressly stated in claim 1, and cannot be ignored by the Office Action.

Accordingly, Engelson teaches applying a polymeric or oligomeric material, in solution with a solvent, to the outer surface of a solid catheter. The polymeric or oligomeric material does not penetrate into the bulk material of the catheter, since the catheter is not disclosed as being porous, absorbent or adsorbent. Instead, the polymeric or oligomeric material in Engelson merely forms a slippery outer surface of the catheter, to assist in its use.

Any teaching of equivalence between ethers, ethanol, methanol and propanol in Engelson is thus limited to the specific context of the invention of Engelson. Engelson does not stand for the proposition that ethers, ethanol, methanol and propanol are equivalent in every context for every use. For example, it is well known that while ethanol can be ingested by humans (and is the key ingredient in most alcoholic beverages), methanol can not be similarly ingested, as it poses serious health risks. Likewise, as described below, Applicants have discovered that all alcohol solvents are not equivalent in the context of the claimed invention. Applicants have discovered that the use of methanol as a solvent for applying the material to the applicator tip, as claimed, results in significant and unexpectedly different properties as compared to the solvents disclosed in Leung, in terms of an unexpectedly superior distribution profile of the material on, and within, the applicator tip.

Accordingly, Engelson's mere disclosure of various solvents for applying a coating to the outer surface of a catheter, would not have motivated one of ordinary skill in the art to use those same solvents in the methods of the claimed invention. Engelson does not teach the equivalency of the solvents for all uses, and Applicants have specifically demonstrated unexpected results. Accordingly, any combination of Engelson and Leung is improper, and would not have rendered obvious the claimed invention.

### 3. The Claimed Invention Provides Unexpected Results

Furthermore, the selection of methanol as a solvent for applying the agent provides unexpected results that are not taught or suggested by the cited references. Such unexpected

results overcome any *prima facie* case of obviousness that may be considered to have been established by the Office Action.

a. The Specification Demonstrates Unexpected Results

As mentioned above, the use of methanol provides an unexpectedly superior distribution profile of the material on, and within, the applicator tip. This different distribution profile, in turn, allows a reduction in tissue damage arising from the highly exothermic polymerization reaction, while providing a lower or equivalent setting time of the dispensed monomeric adhesive. Specification at page 6, lines 2-9.

At most, the cited references teach that a variety of solvents can be used in different applications. Each of Leung and Engelson teach the use of a range of solvents, and each reference at most teaches that the same results would be obtained regardless of the choice of solvent. That is, nowhere does either cited reference teach or suggest that different, improved results would be obtained if one solvent were selected over another solvent. In contrast, the present specification provides express exemplary evidence that different and unexpected results are obtained based on the solvent selection.

At page 9, the present specification describes comparative testing of applicator tips made according to the claimed invention versus applicator tips made according to U.S. Patent No. 5,928,611, which corresponds to the cited WO '797 to Leung. The specification describes that initiator-loaded applicator tips were produced by applying a polymerization initiator or a polymerization rate modifier (benzalkonium chloride) to the tip by pumping a liquid medium comprising the initiator or rate modifier through a syringe and onto the distal end of the tip. Separate initiator-loaded tips were prepared by using a solution of the initiator or rate modifier dissolved in 110  $\mu$ L of various solvents. Page 9, line 28 to page 10, line 9. The tips were prepared using the solvents acetone (disclosed in the Examples of Leung) and methanol (according to the claimed invention).

In the case where acetone was used, the specification describes that different results were obtained when the applicator tips are used to apply a polymerizable cyanoacrylate adhesive material. For example, the specification describes that it can be shown using thermal analysis techniques such as differential scanning calorimetry, that monomer compositions applied through the different applicator tips generate different amounts of heat. If the peak temperature of heat generated is too high, then the heat can be damaging to tissues. Page 9, lines 14-16. For example, as shown in Figure 5, a composition comprising 2-octyl cyanoacrylate dispensed through an applicator tip having an initiator (benzalkonium chloride) applied with acetone generates heat having a peak temperature of about 80°C. Page 9, lines 16-20. However, the same composition dispensed through a tip having the same initiator applied using methanol according to the claimed invention shows a much lower peak temperature of approximately 40°C. Page 9, lines 20-22.

Furthermore, as shown in Figure 6 of the specification, the setting time, or the amount of time required for polymerization, of a 2-octyl cyanoacrylate composition is slightly lower or at least equivalent when the cyanoacrylate composition is dispensed through a tip having a benzalkonium chloride initiator disposed thereon using methanol as compared to using acetone. See specification at Fig. 6 and page 9, lines 23-27.

b. The Previous Rule 132 Declaration of Upvan Narang Confirms the Unexpected Results

Furthermore, the unexpected results provided by the claimed invention were confirmed in the August 7, 2002, Declaration by Upvan Narang, which was previously submitted with the August 13, 2002, Amendment After Final Rejection. A copy of that Declaration is attached hereto for the Examiner's convenience. In the Declaration, a series of tests were described to more specifically isolate the effects of solvent selection on polymerization of the monomer. That is, while the above discussion has focused on the solvent selection in systems having many variables, the testing described in the Declaration

was more specific to demonstrate the different results provided when a different solvent was used to solvate the initiator. See Declaration at paragraph 4.

In the described testing, each of methanol, ethanol and acetone was used to solvate the initiator, and the solvated initiator was mixed with cyanoacrylate to determine the gel set time of the combination. See Declaration at paragraph 5. In the described testing, methanol was selected as the claimed invention; acetone was selected as a representative example of Leung; and ethanol was selected as the closest homolog to methanol and as the solvent relied upon in the previous rejection in the previous Office Action. Incidentally, however, ethanol also corresponds to one of the cited solvents of Engelson, relied upon in the present Office Action.

The position in the Office Action is that the results for methanol and ethanol should be comparable, since they are disclosed as equivalent in Engelson. However, the Declaration proves this assumption of the Office Action to be erroneous. Based on the experiments, the Declaration demonstrates that the use of methanol provides a gel set time of 15.6 minutes, compared to a gel set time of 7.6 minutes for ethanol and 0.4 minutes for acetone. The gel set time for methanol is thus over twice that for ethanol, not comparable as asserted in the Office Action.

Although the mechanisms of why the different results are provided are not known, the data demonstrates that methanol provides results that are significantly different from the results provided by ethanol or acetone. One of ordinary skill in the art, based on the disclosures of Leung and Engelson, would not have expected the significantly different results that are in fact provided by the claimed invention.

c. Conclusion

These results, presented in the present specification, demonstrate that the applicator tips of Leung are different from the applicator tips of the claimed invention, and that the

applicator tips of the claimed invention provide significant and unexpected benefits not disclosed in the cited references.

4. Conclusion

Accordingly, for at least these reasons, the references cannot have rendered obvious to one of ordinary skill in the art the invention of independent claim 1, and the claims dependent therefrom. Reconsideration and withdrawal of the rejection with respect to these claims are respectfully requested.

B. Independent Claim 50

Independent claim 50 is directed to a method of applying at least one agent selected from the group consisting of bioactive materials, flavorants, polymerization initiators, and polymerization rate modifiers to an applicator tip for an adhesive applicator, comprising: dissolving, dispersing or suspending said agent in a liquid medium to form a suspension or solution; combining said suspension or solution and said applicator tip in a vessel; sealing said vessel; applying one of a vacuum or pressure to said vessel to degas air trapped in said applicator tip; releasing said vacuum or pressure; and optionally drying said applicator tip. Such a method is nowhere taught or suggested by the cited references.

The method of claim 50 is directed to an improved method for applying the respective agents to an applicator tip. According to the claimed method, application of the vacuum or pressure results in air that is trapped in the applicator tips being degassed, or forced out of the applicator tips, and being replaced by the solution or suspension including the desired agent. This replacement of air by the solution or suspension thereby loads the material onto or into the applicator tips. Specification at page 11, lines 18-24. The claimed method thus results in an improved loading of the agent into the applicator tip.

In contrast to the claimed invention, Leung merely disclose that "the initiator may be applied to the applicator tip by spraying, dipping, or brushing the applicator tip with a liquid

medium containing the initiator." See Leung at page 17, lines 21-24. Nowhere does Leung teach or suggest that the initiator, or other instantly claimed agent, could or should be applied to the applicator tip by a method specifically utilizing vacuum or pressure to force the agent into the applicator tip.

Engelson does not overcome this deficiency of Leung. Engelson, like Leung, merely teaches dipping the part (a catheter) into the solution of solvent and polymer/oligomer. The Office Action does not cite Engelson for any particular limitation of subject claim 50.

In order for a reference to have rendered obvious the claimed invention, the claimed invention must have been obvious to one of ordinary skill in the art over the cited reference. The motivation to modify the cited references cannot come from Applicants' own disclosure. However, nowhere does either reference teach the use of vacuum or pressure to apply an agent to an applicator tip. Nor does either reference even suggest that such vacuum or pressure could even be used.

The Office Action entirely fails to specify why one of ordinary skill in the art would have been motivated to somehow modify the processes disclosed in the cited references to arrive at the claimed invention. The Office Action does not describe why one of ordinary skill in the art would have substituted the claimed use of vacuum or pressure for the disclosed use of spraying, dipping, or brushing. In the absence of any such teachings, the cited references cannot have rendered obvious the claimed invention.

Accordingly, for at least these reasons, the references cannot have rendered obvious to one of ordinary skill in the art the invention of independent claim 50 and the claims dependent therefrom. Reconsideration and withdrawal of the rejection with respect to these claims are respectfully requested.

C. Conclusion

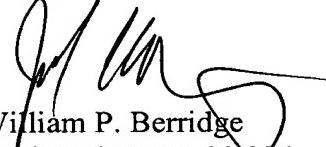
For all of these reasons, Applicants submit that the claimed invention is patentable over the cited references. Reconsideration and withdrawal of the rejection is respectfully requested.

III. Conclusion

In view of the foregoing amendments and remarks, Applicants submit that this application is in condition for allowance. Favorable reconsideration and prompt allowance of the application are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below.

Respectfully submitted,



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Attachment:

Copy of Executed Declaration Under 37 C.F.R. §1.132

Date: February 13, 2004

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